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(54) Title: SMALL PEPTIDE ANAPHYLATOXIN RECEPTOR LIGANDS

(57) Abstract

Oligopeptide compounds or oligopeptide analogue compounds of the formula A-B-D are ligands for the anaphylatoxin receptor and are useful in the treatment of inflammatory disease states; also disclosed are anaphylatoxin receptor ligand compositions and a method for modulating anaphylatoxin activity.

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Small Peptide Anaphylatoxin Receptor Ligands

Technical Field

This invention relates to organic compounds that modulate C5a anaphylatoxin activity. It also relates to methods and compositions for modulating anaphylatoxin activity in human and animal hosts in need of such treatment.

Background of the Invention

A wide variety of conditions including infection by bacteria, viruses or fungi, infiltration by cancer cells, allergic or autoimmune disorders and physically- or chemically-induced trauma causes an inflammatory response in humans. In all of these diseases and conditions in man and in most mammals, activation of the complement system (a set of proteins, regulatory factors and proteolytic enzymes) via either the classical or the alternative pathway, results in the generation of biologically active peptides which serve to amplify and exacerbate the resulting inflammation. The most active peptide, anaphylatoxin C5a, a 74-amino acid polypeptide, is generated by cleavage of the alpha-chain of native C5 at a specific site by convertases (proteolytic enzymes) of the blood complement system as well as by enzymes of the coagulation system. C5a exists *in vivo* in two biologically active forms. Once it is liberated from C5, the carboxyl terminal arginine of C5a is rapidly removed by carboxypeptidase-N, leaving the des-Arg derivative. Although C5a des-Arg is less active than C5a, both are potent inflammatory mediators at concentrations likely to be generated *in vivo* (Fernandez, H. N.; Henson, P. M.; Otani, A.; Hugli, T. E. *J. Immunol.* **1978**, *120*, 109.). Together, these peptides along with C3a, C4a, and their des-Arg degradation products, collectively described herein as anaphylatoxin, are capable of triggering diverse inflammatory reactions.

Among the various cell types, the neutrophil response to C5a is the best defined. Cell surface receptors specific for C5a have been demonstrated on the neutrophil (Chenoweth, D. E.; Hugli, T. E. *Proc. Natl. Acad. Sci. U.S.A* . **1978**, *75*, 3943-3947. Huey, R.; Hugli, T. E. *J. Immunol.* **1985**, *135*, 2063-2068. Rollins, T. E.; Springer, M. S. *J. Biol.*

Chem. **1985**, *260*, 7157-7160.), and the ligand-receptor interaction promotes human polymorpho-nuclear leukocyte (PMN) migration in a directed fashion (chemotaxis), adherence, oxidative burst, and granular enzyme release from these cells (Hugli, T. E. *Springer Semin. Immunopathol.* **1984**, *7*, 193-219.). The interaction of C5a with PMN and other target cells and tissues results in increased histamine release, vascular permeability, smooth muscle contraction, and an influx into tissues of inflammatory cells, including neutrophils, eosinophils, and basophils (Hugli, T. E. *Springer Semin. Immunopathol.* **1984**, *7*, 193-219.). C5a may also be important in mediating inflammatory effects of phagocytic mononuclear cells that accumulate at sites of chronic inflammation (Allison, A. C.; Ferluga, J.; Prydz, H.; Scherlemmer, H. U. *Agents and Actions* **1978**, *8*, 27.). C5a and C5a des-Arg can induce chemotaxis in monocytes (Ward, P. A. *J. Exp. Med.* **1968**, *128*, 1201. Snyderman, R.; Shin, H. S.; Dannenberg, A. C. *J. Immunol.* **1972**, *109*, 896.) and cause them to release lysosomal enzymes (McCarthy, K.; Henson, P. S. *J. Immunol.* **1979**, *123*, 2511.) in a manner analogous to the neutrophil responses elicited by these agents. Recent studies suggest that C5a may have an immunoregulatory role by enhancing antibody particularly at sites of inflammation (Morgan, E. L.; Weigle, W. O.; Hugli, T. E. *J. Exp. Med.* **1982**, *155*, 1412. Weigle, W. O.; Morgan, E. L.; Goodman, M. G.; Chenoweth, D. E.; Hugli, T. E. *Federation Proc.* **1982**, *41*, 3099. Morgan, E. L.; Weigle, W. O.; Hugli, T. E. *Federation Proc.* **1984**, *43*, 2543.).

C5a and C5a des-Arg play important roles in host defenses against bacterial infections and possibly in the mediation of some pathologic lesions such as the leukocyte infiltration seen in the lungs during acute respiratory distress syndrome. This mechanism seems to play a role in different pathological situations like pulmonary distress during hemodialysis, leukophoresis, cardiopulmonary bypass, and in acute myocardial infarction. Complement activation has been postulated to play an important pathological role in rheumatoid arthritis, serum sickness, systemic lupus erythematosus, ulcerative colitis, and forms of hepatic cirrhosis, chronic hepatitis, and glomerulonephritis, in certain shock states, during hemodialysis, and cardiopulmonary bypass, acute

pancreatitis, myocardial infarction (which may be worsened by C5a-induced leuko-embolization following the interaction of complement with atheromatous plaques), asthma, bronchoconstriction, some auto-allergic diseases, transplant rejection, and post-viral encephalopathies.

By serving as antagonists by binding to and blocking the anaphylatoxin receptor, certain compounds of the present invention can reduce or prevent anaphylatoxin-mediated inflammation. Other compounds of the present invention are agonists that mimic anaphylatoxin activity, and assist the body in building its defense mechanism against invasion by infectious agents and malignancy. Additionally, these compounds may influence the immunoregulatory effects of anaphylatoxin. The possible involvement of anaphylatoxin in a wide range of diseases, as indicated by these examples, suggests that anaphylatoxin receptor ligands could have clinical applications for the treatment and prevention of the above-mentioned pathological conditions.

Summary of the Invention

In accordance with the principal embodiment of the present invention, there are provided C5a anaphylatoxin activity modifying compounds of the formula **A-B-D** and the pharmaceutically acceptable salts, esters, or amides thereof.

In the generic formula given above, the groups **B** and **D** may represent a naturally occuring or modified amino acid. These sequences include peptides in which various peptide bonds have been N-alkylated or reduced. In the generic formula given above, the groups **A, B** and **D** have the following values:

A is R_1-R_2;
B is R_3-R_4-R_5; and
D is R_6-R_7-R_8.

The group R_1 is selected from the group consisting of lower alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylhydrazino, arylalkylamino, aminoalkyl, arylalkenyl, heterocyclic, (heterocyclic)alkyl and hydrogen.

R_2 is selected from the group consisting of >C=O, >C=S, $>CH_2$ and $>SO_2$ with the proviso that when R_2 is >C=S or $>SO_2$, then R_1 cannot be hydrogen.

R_3 and R_6 are independently selected from the group consisting of $>N\text{-}R_{101}$ where R_{101} is selected from hydrogen, lower alkyl or arylalkyl.

R_4 is selected from the group consisting of $-CR_{200}R_{201}-$, $>NR_{101}$, and $>C=CHR_{205}$, existing in either the *Z*- or *E*-configuration where R_{205} is arylalkyl.

R_5 is selected from the group consisting of >C=O, $>CH_2$, and $-CH_2\text{-}C(O)-$.

R_7 is $-CR_{210}R_{211}-$.

R_8 is selected from the group consisting of -H, $-CH_2\text{-}CO_2H$ or $>CO_2R_{100}$ where R_{100} is selected from the group consisting of hydrogen, lower alkyl and arylalkyl.

R_{200} and R_{210} are independently selected from the group consisting of hydrogen, lower alkyl and arylalkyl.

R_{201} is selected from the group consisting of

(a) $-(CH_2)_3\text{-}Z$ where Z is aryl or heterocyclic with the proviso that when Z is heterocyclic, the point of attachment of the $-(CH_2)_3-$ moiety to Z is a ring carbon atom;

(b) $-CH_2\text{-}X\text{-}CH_2\text{-}Z$, where X is selected from the group consisting of >O, >S, and >N-R where R is hydrogen or lower alkyl, and Z is as defined above with the proviso that when Z is heterocyclic, the point of attachment of the $-CH_2\text{-}X\text{-}CH_2-$ moeity to Z is a ring carbon atom,

(c) $-CH_2\text{-}S\text{-}CHR_{300}\text{-}W$ where W is aryl and R_{300} is selected from carboxy, alkoxycarbonyl and alkyl,

(d) $-CH_2\text{-}CH_2\text{-}X\text{-}W$, where X and W are as defined above,

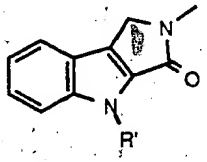
(e) $-CH_2\text{-}C(O)\text{-}NR\text{-}W$, where W and R are as defined above, and

(f) $-CH_2-Y-C(O)-Z$, where Y is selected from >O and >N-R and Z and R are as defined above with the proviso that when Z is heterocyclic, the point of attachment of the $-CH_2-C(O)-$ moiety to Z is a ring carbon atom.

R_{211} is guanidinoalkyl.

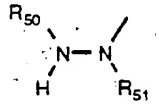
R_1 and R_2, taken together, optionally represent hydrogen, lower alkyl, arylalkyl, aminoalkyl or guanidinoalkyl with the proviso that when R_1 other than arylalkyl, then R_{101} must be arylalkyl.

R_1-R_2-R_3, taken together, optionally may represent a compound of the formula:



where R' is selected from hydrogen or loweralkyl.

R_1-R_2-R_3-R_4, taken together, optionally may represent aryl, arylalkylamino, heterocyclic, arylalkyl or a compound of the formula:



where R_{50} is aroyl and R_{51} is selected from aryl and arylalkyl.

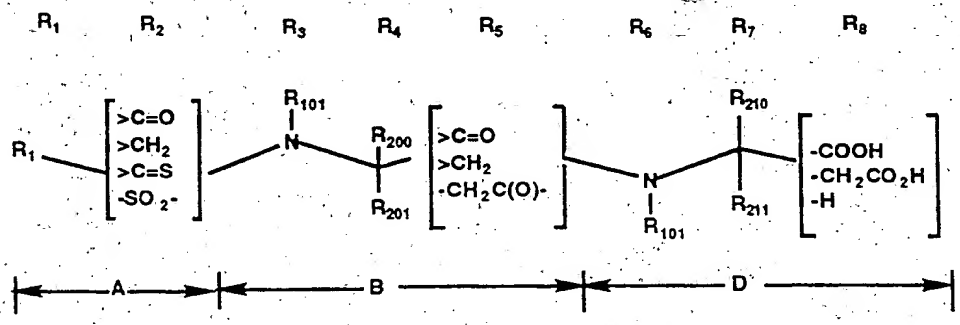
The present invention also relates to a method for modulating C5a anaphylatoxin activity in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1.

The invention further relates to anaphylatoxin modulating compositions comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of Claim 1.

Detailed Description

As discussed above, C5a is the most active of a class of biologically active peptides which serves to amplify and exacerbate inflammation. While C5a contains 74 amino acid residues, it has been found in accordance with the present invention that oligopeptides containing as few as two amino acid residues are also actively bound by C5a receptors. Moreover, it has been found that peptidomimetic compounds (i.e. compounds which mimic the activity of peptides) in which certain groups replace the α-carbon, carbonyl group, and amide-nitrogen group of the individual amino acids in oligopeptides are also actively bound by C5a receptors.

The chemical structures of the compounds of the present invention are best understood by reference to the following structural formula in which it is understood that the segments are joined serially at the free valence bonds to form the compound **A-B-D**



As used throughout this specification and the appended claims, the following terms have the meanings specified.

The term "alkyl" as used herein refers to monovalent straight chain or branched chain groups of 1 to 12 carbon atoms, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, *tert*-butyl and the like.

The term "lower alkyl" as used herein refers to straight or branched chain alkyl groups containing from 1 to 8 carbon atoms including but not limited to methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, 2-methylhexyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "alkenyl" as used herein refers to straight or branched chain groups of 2 to 12 carbon atoms containing a carbon-carbon double bond, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like, wherein the alkenyl group may be substituted with alkylcarbonylamino, cyano, carboxy, hydroxyalkyl and the like.

The term "alkoxy" as used herein refers to an alkyl group as defined above, attached to the remainder of the molecule through an oxygen atom. Alkoxy groups include, for example, methoxy, ethoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, *tert*-butoxy and the like.

The term "alkoxycarbonylalkyl" as used herein refers to an alkoxy group, as previously defined, appended to an alkyl group, as previously defined, through a carbonyl group. Alkoxycarbonylalkyl includes, but is not limited to methoxycarbonylmethyl, ethoxycarbonylmethyl, methoxycarbonylethyl and the like.

The term "alkylcarbonylaminoalkyl" as used herein refers to an alkyl group as previously defined appended to an aminoalkyl group as defined below through a carbonyl group. Alkylcarbonylaminoalkyl includes, but is not limited to, acetylaminopropyl, acetylaminomethyl and the like.

The term "amino" as used herein refers to a group having the structure $-NR_{342}R_{343}$. The groups R_{342} and R_{343} are independently selected from hydrogen, lower alkyl, aryl and arylalkyl. Additionally, R_{342} and R_{343} taken together, may optionally be $-(CH_2)_{mm}-$ where mm is an integer of from 2 to 6. Amino includes, but is not limited to H_2N-, methylamino, dimethylamino, benzylamino, piperidinyl, N-benzyl-N-(3-phenylpropyl)amino, N-(2-phenylethyl)-N-(3-phenylpropyl)amino, N-(4-phenylbutyl)-N-(3-phenylpropyl)amino and the like.

The term "aminoalkyl" as used herein refers to an amino group as previously defined appended to a lower alkyl group, as previously defined. Aminoalkyl includes, but is not limited to aminomethyl, 3-aminopropyl, benzylaminomethyl, N-(2-phenylethyl)aminoethyl, N-benzyl-N-methylaminomethyl, N-(2-phenylethyl)-N-ethylaminoethyl and the like.

The term "aminoalkylcarbonyl" as used herein refers to an aminoalkyl group appended to the parent molecular moiety through a carbonyl group. Aminoalkylcarbonyl includes, but is not limited to, 6-aminohexanoyl, 5-aminopentanoyl and the like.

The term "aminocycloalkyl" as used herein refers to an amino group, as previously defined, appended to a cycloalkyl group, as previously defined. Aminocycloalkyl includes, for example, 4-aminocyclohexan-1-yl, 3-aminocyclopentan-1-yl, 4-(N-benzylamino)cyclohexan-1-yl and the like.

The term "aryl" as used herein refers to substituted and unsubstituted carbocyclic aromatic groups including, but not limited to phenyl, 1- or 2-naphthyl, fluorenyl, (1,2)-dihydronaphthyl, (1,2,3,4)-tetrahydronaphthyl, indenyl, indanyl and the like, wherein the aryl group may be substituted with 1, 2, or 3 substituents independently selected from alkoxycarbonyl, amino, aminoalkyl, arylalkoxy, aryloxy, halo, nitro, carboxy, cyano, C_1 to C_{12} alkyl, alkoxy, aroyl, hydroxy, sulfonamido and halosubstituted alkyl. When the substituent is fluorine, there may be up to five fluorines on phenyl. Also included in the definition are compounds such as 4-methyl-2,3,5,6-tetrafluorophenyl.

The term "arylalkenyl" as used herein refers to an aryl group, as previously defined, appended to an alkenyl group, as previously defined, including, but not limited to 2-phenyl-ethen-1-yl, 2-phenyl-1-cyano-ethen-1-yl, 2-(2-aminophenyl)-ethen-1-yl, 2-phenyl-1-acetamido-ethen-1-yl and the like.

The term "arylalkoxy" as used herein refers to an arylalkyl group as previously defined, attached to the parent molecular moiety through an oxygen atom. Arylalkoxy includes, but is not limited to benzyloxy, 2-phenethyloxy, 1-naphthylmethyloxy and the like.

The term "arylalkoxyalkyl" as used herein refers to an arylalkoxy, group as previously defined, attached to an alkyl group, as previously defined. Arylalkoxyalkyl includes, but is not limited to benzyloxymethyl, 2-phenethyloxymethyl, 1-naphthylmethyloxy and the like.

The term "arylalkyl" as used herein refers to an aryl group, as previously defined, appended to an alkyl group, including, but not limited to benzyl, 1- and 2-naphthylmethyl, halobenzyl, alkoxybenzyl,

hydroxybenzyl, aminobenzyl, nitrobenzyl, guanidinobenzyl, phenylmethyl(benzyl), 1-phenylethyl, 2-phenylethyl, 1-naphthylethyl and the like.

The term "arylalkylamino" as used herein refers to a group having the structure -NHR$_{442}$ or -NHR$_{442}$R$_{443}$. The groups R$_{442}$ and R$_{443}$ are independently selected from arylalkyl as previously defined. Examples include benzylamino, N-benzyl-N-(3-phenylpropyl)amino, N-(2-phenylethyl)-N-(3-phenylpropyl)amino, N-(4-phenylbutyl)-N-(3-phenylpropyl)amino and the like.

The term "aminocarbonylalkyl" as used herein refers to an amino group, as previously defined, appended to an alkyl group, as previously defined, through a carbonyl group. Examples included dimethylaminocarbonylmethyl, dimethylaminocarbonylethyl, aminocarbonylmethyl and the like.

The term "arylcarbonylaminoalkyl" as defined herein refers to an aryl group, as previously defined, appended to an aminoalkyl group, as previously defined, through a carbonyl group. Examples include, 3-(benzoylamino)propyl, 2-(benzoylamino)ethyl, benzoylaminomethyl and the like.

The term "aryloxy" as used herein refers to an aryl group as previously defined, attached to the parent molecular moiety through an oxygen atom. Aryloxy includes, but is not limited to phenoxy, 1-naphthoxy, 2-naphthoxy and the like.

The term "aroylaminoalkyl" as used herein refers to an aroyl group as defined above, appended to an aminoalkyl group, as previously defined. Examples include benzoylaminomethyl and substituted benzoylaminomethyl.

The term "aroyl" as used herein refers to an aryl group as defined above, attached to the parent molecule through a carbonyl group. Examples include benzoyl and substituted benzoyl.

The term "benzyl" as used herein refers specifically to to phenyl substituted methyl in which the phenyl group may be substituted with 1, 2 or 3 substituents independently selected from halo, nitro, cyano, alkyl of from one to twelve carbon atoms, alkoxy, aroyl and halosubstituted alkyl and the like.

The term "carboxyalkyl" as used herein refers to a carboxyl group, $-CO_2H$, appended to a lower alkyl group, as previously defined.

The term "(carboxyamido)alkyl" as used herein refers to a group of the formula $-C(O)NR_{346}R_{347}$, appended to a lower alkyl group, as previously defined. The groups R_{346} and R_{347} are independently selected from hydrogen, lower alkyl, aryl and arylalkyl. Alternatively, R_{340} and R_{341} taken together may optionally be $-(CH_2)_{pp}-$ wherein pp is an integer of from 2 to 6.

The term "cyanoalkyl" as used herein refers to a cyano group, $-C\equiv N$, appended to a lower alkyl group, as previously defined.

The term "cycloalkyl" as used herein refers to cyclic groups, of 3 to 8 carbons, including, but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, wherein the cycloalkyl group may be substituted with 1, 2 or 3 substituents independently selected from amino, aryl, halo, nitro, carboxy, cyano, C_1 to C_{12} alkyl, alkoxy, aroyl, guanidino, sulfonamido and halosubstituted alkyl.

The term "(cycloalkyl)alkyl" as used herein refers to a cycloalkyl group appended to a lower alkyl group, including, but not limited to cyclohexylmethyl and cyclohexylethyl.

The term "guanidinoalkyl" as used herein refers to a group of the structure $-NR_{352}C(=NR_{353})NHR_{354}$ appended to a lower alkyl group, as previously defined. R_{352}, R_{353} and R_{354} are independently selected from hydrogen, lower alkyl and aryl.

The term "heterocyclic" as used herein refers to any 5- or 6-membered ring containing from one to three heteroatoms independently selected from the group consisting of one nitrogen, oxygen, or sulfur, one oxygen and one nitrogen, one sulfur and one nitrogen, and one, two or three nitrogen; wherein the 5-membered ring has 0 to 2 double bonds and the 6-membered ring has 0 to 3 double bonds, wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, wherein the nitrogen heteroatom may optionally be quaternized. The term "heterocyclic" also includes bicyclic groups in which any of the above heterocyclic rings is fused to a benzene ring or cyclohexane ring or another heterocyclic ring (for example, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl or benzothienyl and the like). Representative heterocycles include, but

are not limited to pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazoyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl and thienyl.

Heterocyclics can be unsubstituted or substituted with 1, 2, or 3 substituents independently selected from amino, halo, hydroxy, nitro, carboxy, cyano, C_1 to C_{12} alkyl, alkoxy, aroyl, oxo (=O), sulfonamido, arylcarbonylaminoalkyl, aminoalkyl, alkoxycarbonylalkyl, alkylcarbonylaminoalkyl, guanidinoalkyl, (heterocyclic)alkylcarbonylaminoalkyl, arylalkyl, aminoalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, halosubstituted alkyl and (AA)aminoalkyl where AA refers to a naturally occuring amino acyl (a naturally occuring amino acid in which the C-terminal -OH has been removed) or modified amino acyl (a modified amino acid in which the C-terminal -OH has been removed) compound such as ornithinyl, 2-amino-5-phenylpentanoyl or 2-amino-3-cyclohexylpropanoyl and the like which is coupled to aminoalkyl group, as previously defined, through an amide linkage (-C(O)-NR_{101}-) where R_{101} is hydrogen, lower alkyl or arylalkyl. In addition, nitrogen containing heterocycles can be N-protected.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group, as previously defined, appended to a lower alkyl group as previously defined.

The term "(heterocyclic)alkylcarbonylaminoalkyl" as used herein refers to a heterocyclic group, as previousl defined, appended to an aminoalkyl group as defined herein through a carbonyl group. (Heterocyclic)alkylcarbonylaminoalkyl includes but is not limited to imidazol-4-ylmethylcarbonylaminopropyl.

The term "hydrazino" as used herein refers to a hydrazino group R_{50}NH-NR_{51}- where R_{50} is selected from aryl and aroyl and R_{51} is selected from hydrogen, aryl and arylalkyl. Examples include 2-(3-fluorobenzoyl)-1-(3-phenylpropyl)hydrazino, 2-(3-fluoro-4-methylbenzoyl)-1-(3-phenylpropyl)hydrazino and the like.

The term "hydroxyalkyl" as used herein refers to a hydroxy group, -OH, appended to a lower alkyl group, as previously defined.

The term "naturally occuring amino acid" refers to an amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

The term "N-terminal protecting group" or "N-protected" refers to those groups intended to protect the N-terminus or an amino group against undesirable reactions during synthetic procedures or to prevent the attack of exopeptidases on the final compounds or to increase the solubility of the final compounds and includes, but is not limited to acyl, acetyl, pivaloyl, *tert*-butylacetyl, *tert*-butyloxycarbonyl (Boc), carbobenzyloxycarbonyl (Cbz), benzoyl groups or an L- or D-aminoacyl residue, which may itself be N-protected similarly. Other groups may be found in Volume 3 of *The Peptides*, E. Gross and J. Meienhofer, Academic Press, 1981.

The term "anaphylatoxin" is used herein to mean C5a, C4a, C3a or the corresponding des-Arg degradation products.

By "pharmaceutically acceptable salt" it is meant those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art . For example, S. M Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, **1977**, *66*:1 - 19 . The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate,

lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium; lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like.

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1 to C_6 alkyl esters wherein the alkyl group is straight or branched chain. Acceptable esters also include C_5 to C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C_1 to C_4 alkyl esters are preferred. Esters of the compounds of this invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C_1 to C_6 alkyl amines and secondary C_1 to C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5 or 6 membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1 to C_3 alkyl primary amides and C_1 to C_2 dialkyl secondary amides are preferred. Amides of the compounds of this invention may be prepared according to conventional methods.

Asymmetric centers may exist in the compounds of the present invention. The present invention contemplates the various stereoisomers and mixtures thereof. In particular, chiral centers can exist at R_4 and R_7.

Particular stereoisomers are prepared by selecting the starting amino acids or amino acid analogs having the desired stereochemistry and reacting these starting materials by the methods detailed below. Starting compounds of particular stereochemistry are either commercially

available or are made by the methods detailed below and resolved by techniques well known in the organic chemical arts.

One class of preferred compounds of the present invention are those in which the groups R_3 and R_6 are independently selected from >NH and >N-Methyl.

In another class of preferred compounds of the present invention, the group R_5 is selected from >C=O and $>CH_2$.

In another class of preferred compounds of the present invention, the group R_4 is $-CR_{200}R_{201}-$.

In one preferred class of compounds of the present invention, **B** is 2-Amino-5-phenylpentanoyl.

In another class of preferred compounds of the present invention, **D** is Arginyl-OH.

In yet another class of preferred compounds of the present invention, **B** is 2-Amino-5-phenylpentanoyl and **D** is Arginyl-OH.

Another class of preferred compounds of the present invention are those in which the chirality of 2-Amino-5-phenylpentanoyl is *R*.

Representative examples of a preferred class of compounds of this invention where **D** is Arginyl-OH, include the following compounds, as well as their pharmaceutically acceptable salts, esters, and amides:

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-2-fluorobenzyl)-Arginyl-OH;

N-{N-Benzyl-N-(3-phenylpropyl)amino-carbonyl}-Arginyl-OH;

N-{N-2-Phenylethyl-N-(3-phenylpropyl)amino-carbonyl}-Arginyl-OH;

N-{N-(4-Phenylbutyl)-N-benzylamino-carbonyl}-Arginyl-OH;

N-{[2-(3-Fluoro-4-methylbenzoyl)-1-(3-phenylpropyl)hydrazino]-carbonyl}-

Arginyl-OH;

N-(Indole-2-carbonyl)-DCysteinyl(S-benzyl)-Arginyl-OH;

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-3-methylbenzyl)-Arginyl-OH;

N-{[2-(3,4-Difluorobenzoyl)-1-(3-phenylpropyl)hydrazino]-carbonyl}-Arginyl-

OH;

N-(Indole-2-carbonyl)-DCysteinyl(S-4-fluorobenzyl)-Arginyl-OH;

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-2-methylbenzyl)-Arginyl-OH;

N-(Indole-2-carbonyl)-DCysteinyl(S-3-fluorobenzyl)-Arginyl-OH;

N-{N-(4-Phenylbutyl)-N-(3-phenylpropyl)amino-carbonyl}-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-4-methylbenzyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-4-chlorobenzyl)-Arginyl-OH;
N-{[2-(3,5-Dichlorobenzoyl)-1-(3-phenylpropyl)hydrazino]-carbonyl}-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-3-chlorobenzyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-2-chlorobenzyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl-DCysteinyl(S-benzyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-1-naphthylmethyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-3-aminobenzyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-4-aminobenzyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-cyclohexylmethyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-3-nitrobenzyl)-Arginyl-OH; and
N-(Indole-2-carbonyl)-{(*R/S*)-2-Amino-4-phenoxybutanoyl}-Arginyl-OH.

In another preferred embodiment of the present invention **B-D** taken together are {2-Amino-5-phenylpentanoyl}-Arginyl-OH. Representative examples of this embodiment include the following compounds, as well as their pharmaceutically acceptable salts, esters, and amides:
N-(5-Methoxyindole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-[1-(3-Benzoylaminopropyl)-Indole-2-carbonyl]-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(1-Naphthylcarbonyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(5-Fluoroindole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(1-[N-{(2R)-2-Amino-3-cyclohexylpropanoyl}aminopropyl]-indole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(Pyrrole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-DLArginyl-OH;
N-Benzoyl-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3,4-Dimethylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(5-Chloro-indole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;

N-[1-(3-Aminopropyl)-indole-2-carbonyl]-{(*R*)-2-Amino-5-phenyl-pentanoyl}-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(Indole-2-carbonyl)-(N-Methyl){(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3,4-Dichlorobenzyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(Indole-2-carbonyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
{(*R*)-2-(1,2,3,4-Tetrahydro-3-oxopyrrole[3.4.b]indole-2-yl)-5-phenylpentanoyl}-Arginyl-OH;
N-(2-Naphthylcarbonyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(1-tert-Butyloxycarbonylmethylindole-2-carbonyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(4-Phenylpyrrole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-{1-(3-Acetylaminopropyl)indole-2-carbonyl]-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(1-Benzylindole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-[1-(3-Guanidinopropyl)indole-2-carbonyl]-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-{1-[3-(Imidazol-4-ylmethylcarbonylamino)propyl]-indole-2-carbonyl}-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(4-Methylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3-Chlorobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(4-Chlorobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3,5-Difluorobenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(2-Fluorobenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3,4-Difluorobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(4-Fluorobenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3-Fluorobenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(4-tert-Butylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3-Chloro-4-methoxybenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3-Chloro-4-methylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;

N-(Indole-4-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(Indole-5-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3-Fluoro-4-methylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(Indole-3-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3-Chloro-4-fluorobenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3-Iodo-4-methylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3-Iodobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(4-Phenylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(1-Methylindole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(Benzofuran-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3-Bromo-4-methylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(Pyrrole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3-Bromobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-(3-Oxo-2-phenylpyrazole-5-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH;
N-{1-[3-(2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonylamino)propyl]-indole-2-carbonyl}-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH; and
N-(Indole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-(N-Methyl)-Arginyl-OH.

Method of Treatment

The compounds of the present invention serve to modulate the activity of C5a anaphylatoxin. Certain compounds of the present invention function as anaphylatoxin antagonists, while others function as agonists. The antagonist compounds of the present invention block the anaphylatoxin receptor and prevent anaphylatoxin activity, which makes those compounds useful in the treatment and prevention of injurious conditions or diseases in which anaphylatoxin may be involved. Disease

states in which anaphylatoxin is involved include asthma, bronchial allergy, chronic inflammation, systemic lupus erythematosus, vasculitis, serum sickness, angioedema, rheumatoid arthritis, osteoarthritis, gout, bullous skin diseases, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, immune complex-mediated glomerulonephritis, psoriasis, allergic rhinitis, adult respiratory distress syndrome, acute pulmonary disorders, endotoxin shock, hepatic cirrhosis, pancreatitis, inflammatory bowel diseases (including Crohn's disease and ulcerative colitis), thermal injury, Gram-negative sepsis, necrosis in myocardial infarction, leukophoresis, exposure to medical devices (including but not limited to hemodialyzer membranes and extracorpeal blood circulation equipment), chronic hepatitis, transplant rejection, post-viral encephalopathies, and/or ischemia induced myocardial or brain injury. These compounds may also be used as prophylactics for such conditions as shock accompanying Dengue fever. In addition, a combination of antibiotic and anti-inflammatory agent such as corticosteroids (e.g., methylprednisolone) and one or more of the above mentioned compounds may be employed.

Certain compounds of the invention are useful therapeutic agents because of their ability to mimic or promote anaphylatoxin activity and are therefore useful in stimulating the inflammatory response and immune response in mammals who are deficient in this regard. These agonist compounds may be used to assist the body in building its defense mechanism against invasion by infectious microorganisms or other stress. Interaction by these agonists at the anaphylatoxin receptor makes them useful in treating conditions or diseases including, but not limited to cancers (such as lung carcinoma), immunodeficiency diseases, and severe infections.

In some cases this will involve preventing the underlying cause of the disease state and in other cases, while the underlying disease will not be affected, the compounds of this invention will have the benefit of ameliorating the symptoms or preventing the manifestations of the disease.

The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants and vehicles as desired.

The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intrasternal, intra-arterial injection or infusion techniques, without limitation. The term "topically" encompasses administration rectally and by inhalation spray, as well as by the more common routes of the skin and the mucous membranes of the mouth and nose.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to achieve the desired therapeutic response for a particular patient, compositions, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

Generally dosage levels of about 0.001 mg to about 100 mg, more typically from about 0.1 mg to about 20 mg, of active compound per kilogram of body weight per day are administered daily to a mammalian host. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, e.g. two to four separate doses per day.

Formulation of Pharmaceutical Composition

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous cariers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the

like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like, Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay abdorption such as aluminum monostearate and gelatin.

If desired, and for more effective distribution, the compounds can be incorporated into slow release or targeted delivery systems such as polymer matrices, liposomes, and microspheres.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternaryammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as

kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose,

aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers, or propellants which may be required. Opthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Anaphylatoxin Receptor Binding K_i Determination

Specific inhibition of C5a binding activity of representative compounds of the present invention was measured using 0.03-1 nM ^{125}I-C5a with 2.5-25 µg/mL of purified PMNL membrane fragments (Borregaard, N.; Heiple, J.M.; Simons, E.R.; and Clark, R.A. *J. Cell. Biol.* **1983,** *97*, 52-61.). Free and membrane-bound ligand were separated by filtration. Binding potencies for representative examples of compounds of this invention are listed in Table 1.

Table 1

In vitro C5a Receptor Binding Potency of Compounds of this Invention

Example	K_i µM	Example	K_i µM
10	3.8	15	1.97
20	16	25	15.5
26	2.2	29	3.0
31	2.1	33	0.56
41	6.2	58	1.20

61	2.4	68	0.63
70	3.34	72	28
81	1.3	87	26
95	48	99	3.8
107	111	113	0.8
130	12	133	5.95
133	5.95	141	170
141	170	143	90
152	1.96	154	1.0

Synthesis of the Compounds

The novel compounds and salts thereof of the invention can be utilized effectively as therapeutic agents. Accordingly, the present invention further relates to therapeutic compositions comprising a novel compound having the general formula I or salts thereof as an active component.

The compounds of the invention may be prepared by a synthetic method of elongation of a peptide chain through condensation of one amino acid by one, or by a method of coupling fragments consisting of two or several amino acids, or by a combination of these methods in accordance with conventional peptide synthesis methods.

The condensation of two amino acids, the condensation of an amino acid with a peptide or the condensation of one peptide with another peptide may be effected in accordance with conventional condensation methods such as azide method, mixed acid anhydride method, symmetrical anhydride method, DCC (dicyclohexylcarbodiimide) method, active ester method (p-nitrophenyl ester method, N-hydroxysuccinimide ester method, cyanomethyl ester method and the like), Woodward reagent K method, dicyclohexylcarbodiimide/1-hydroxy©24
benzotriazole (DCC-HOBT) method and the like. These condensation reactions may be done by either solution methods or solid phase synthetic methods. When the peptide chain is elongated by the solid phase method, the C-terminal amino acid is linked to an insoluble carrier.

As the insoluble carrier, any that can produce a detachable bond by reacting with a carboxyl group in a C-terminal amino acid may be used, and the examples thereof involve, for example, halomethyl resins such as chloromethyl resin, bromomethyl resin and the like, hydroxy-methyl resin, benzhydrylamine resin, and *t*-alkyloxycarbonyl hydrazide resin.

As conventional polypeptide synthesis, branched chain amino and carboxyl groups at alpha and omega positions in amino acids may be protected/deprotected if necessary. The protecting groups for amino groups which can be used involve, for example, benzyloxycarbonyl (Z), *o*-chlorobenzyloxycarbonyl ((2-C1)Z), p-nitrobenzyloxycarbonyl ($Z(NO_2)$), *p*-methoxy-benzyloxycarbonyl (Z(OMe)), *t*-butoxycarbonyl (Boc), *t*-amyloxycarbonyl (Aoc), isobornyloxycarbonyl, admantyloxycarbonyl, 2-(4-biphenyl)-2-propyloxycarbonyl (Bpoc), 9-fluorenyl-methoxycarbonyl (Fmoc), methylsulfonylethoxycarbonyl (Msc), trifluoroacetyl, phthalyl, formyl, 2-nitrophenylsulfenyl (Nps), diphenylphosphinothioyl (Ppt), and dimethylphosphinothioyl (Mpt).

The examples of protecting groups for carboxyl groups involve, for example, benzyl ester (OBn), cyclohexyl ester, 4-nitrobenzyl ester ($OBnNO_2$), *t*-butyl ester (O*t*Bu), 4-picolyl ester (OPic) and the like.

In the course of the synthesis of the present novel compounds, specific amino acids having functional groups other than amino and carboxyl groups in the branched chain such as arginine, cysteine, serine, and the like may be protected, if necessary, with suitable protecting group. It is preferable that for example, the guanidino group (N^G) in arginine may be protected with nitro, p-toluenesulfonyl (Tos), benzyloxycarbonyl (Z), adamantyloxycarbonyl (Adoc), p-methoxybenzenesulfonyl, 4-methoxy-2,6-dimethylbenzene-sulfonyl (Mds), 1,3,5-trimethylphenylsulfonyl (Mts) and the like, and the thiol group in cysteine may be protected with benzyl, p-methoxybenzyl, triphenylmethyl, acetamidomethyl, ethylcarbamyl, 4-methylbenzyl (4-MeBn), 2,4,6-trimethylbenzyl (Tmb) and the like, and the hydroxyl group in serine may be protected with benzyl (Bn), t-butyl, acetyl, tetrahydropyranyl and the like.

(N-Boc)-(2*R*)-2-Amino-3-cyclohexylpropanoic acid: A solution of Boc-D-phenylalanine (50 g, 0.19 mol) in methanol (500 mL) was hydrogenated at ambient temperature at 4 atmospheres with 5% rhodium on alumina (5.0 g). Removal of catalyst by filtration and evaporation yielded the product quanititatively. The (2*S*)-isomer was prepared in an identical manner from Boc-L-phenylalanine.

The compounds of the invention were prepared by standard solid phase peptide synthesis conditions as described in "Solid Phase Peptide Synthesis" by J. M. Stewart and J. D. Young, Second Edition (1984) and illustrated in Examples 1 and 2 in the experimental section.

The compounds of the invention may also be prepared by partial solid phase synthesis, fragment condensation methods and classical solution methods as exemplified by the methods described in "Peptide Synthesis", Second Edition, M. Bodanszky, Y. S. Klausner, and M. A. Ondetti (1976).

The standard chirality descriptors "*R*" and "*S*" are used to indicate an isomerically pure center, "*RS*" to indicate a mixture, and "*R/S*" to indicate a single pure isomer of undetermined configuration. The descriptor "±" refers to a d,l mixture of amino acids at the indicated residue.

The foregoing may be better understood by reference to the following examples which are provided for illustration and not limitation of the practice of the invention. Unless otherwise indicated, the standard peptide methods described above and in Examples 1 and 2 are used to assemble the different products, using the precursors indicated by the specific peptide sequence. The synthetic products were at least 95% pure, and gave NMR and mass spectra consistent with the desired product.

Example 1

Preparation of H-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl(N-guanidino-Tos)-Merrifield Resin

Boc-Arg(N-guanidino-Tos)-Merrifield resin (0.4-1.0 g) was placed in a solid phase peptide synthesis vessel and Boc-(*R*)-2-Amino-5-phenylpentanoic Acid was attached to the resin, according to the protocol outlined in Agenda A to yield the protected peptide resin: H-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl(N-guanidino-Tos)-Merrifield Resin.

Following the synthesis, the protected peptide resin was removed from the reaction vessel by washing the resin three times with 20 mL DMF into a 30-60 mL sintered glass funnel, followed by washing the resin three times with 20 mL methylene chloride. The resin was dried at least five hours, then weighed.

Agenda A

1. Deblock: 45 % trifluoroacetic acid (TFA) in methylene chloride containing 2.5 % anisole (v/v/v).
2. Neutralization: 10 % diisopropylethylamine (DIEA) in methylene chloride (v/v).
3. Single Coupling: 0.2-0.4 *M* Boc-amino acid derivative in N,N-dimethylformamide (DMF), 0.2-0.4 *M* diisopropylcarbodiimide (DIC) in methylene chloride, reaction time, 60 minutes.
4. Resin base washing: 10 % DIEA in methylene chloride (v/v).
5. Single Coupling repeated: same as Step 3.
6. Go to next residue, i.e. **A** (go back to Step 1).

Example 2

Preparation of H-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

The protected pepetide resin of Example 1 (600 mg) was treated with 1.0 mL of anisole and 10 mL of hydrogen fluoride (HF) for 60 minutes at 0 °C. The HF and anisole were removed *in vacuo* at 0 °C, and the mixture of the pepetide and resin was washed with diethyl ether (2 x 25 mL). The crude pepetide was extracted from the mixture by treatment with portions of 20% aqueous acetic acid (4 x 25 mL), lyophilized to a dry

amorphous powder, and purified by high performance liquid chromatography (HPLC) (column 21.4 mm ID x 25 cm or 41.4 mm ID x 25 cm, Dynamax (Rainin), 8 μm silica, C18 reverse-phase column). The sample was purified by gradient elution {from 20 to 60% (80% acetonitrile in water with 0.1% trifluoroacetic acid)} at a flow rate of 15-45 mL/minute.

Example 3

Preparation of 2-(*R*)-Amino-5-phenylpentanoic acid

(±)-2-Amino-5-phenylpentanoic acid (35 g) was suspended in water (3 L) and solubilized by adjusting the pH to 12 with 7 N sodium hydroxide solution. The pH was readjusted to pH 8 using 1 M phosphoric acid with continuous stirring at 45 °C. The solution was allowed to cool to 40 °C and L-amino acid oxidase (Sigma, 0.7 unit/mg) was added. The reaction was stirred with good aeration at 37-40 °C for two weeks. The reaction was monitored using the following High Pressure Liquid Chromatography (HPLC) system: C-18 Waters analytical column, 20% acetonitrile in Buffer (0.624 g/L $CuSO_4 \cdot 5H_2O$, 0.576 g/L L-proline, 2 g/L ammonium acetate, and 1L of water with the pH of the solution adjusted to pH 7 with ammonium hydroxide); 2 mL/minute flow rate; fluorescence detection: Ex 345 nm, Em>415 nm; OPA derivatization: 300 μL of 1 N sodium borate pH 9.4, 50 mL of 20 mg *ortho*-phthalaldehyde (OPA) plus 24 ng N-acetyl cysteine/6 mL 50% methanol/water; incubate 3 minutes at ambient temperature. When the digestion of the L-enantiomer was complete, the reaction mixture was concentrated to 500 mL by removing water *in vacuo*. The pH was adjusted to 5 and the precipitate was collected by filtration and recrystallization from ethanol-water to afford 17.32 g (99%) of the title compound.

Example 4

Preparation of (±)-2-Amino-5-phenylpentanoic acid

Diethyl acetamidomalonate (220 g) in 1 L of absolute ethanol was added to a stirred solution of sodium ethoxide in ethanol, prepared by dissolving sodium (24 g) in absolute ethanol (500 mL), under nitrogen. The reaction mixture was refluxed under nitrogen for 30 minutes and then 1-bromo-3-phenylpropane (200 g) was added. The reaction mixture was

refluxed overnight, cooled to ambient temperature, the precipitate removed by filtration and the solvent removed *in vacuo*. Concentrated hydrochloric acid (800 mL) was added to the residue and the reaction mixture was refluxed for 14 hours. The cooled aqueous solution was washed with ether (2 x 200 mL). The residual ether in the aqueous phase was removed by nitrogen bubbling through the solution. The pH of the aqueous phase was adjusted to 7-8 by the addition of ammonium hydroxide. The title compound was collected by filtration, air dried and recrystallized from ethanol-water to afford 150 g (83%). m.p. 255-257 °C. MS (FAB) m/e 194 $(M+H)^+$.

Example 5

Preparation of Boc-2-(*R*)-Amino-5-phenylpentanoic acid

Di-*tert*-butyl dicarbonate (15 g) in 50 mL of *tert*-butanol was added dropwise to a stirred solution of 2-(*R*)-amino-5-phenylpentanoic acid (9 g) dissolved in 50 mL of 1 N sodium hydroxide solution. The solution was stirred at ambient temperature overnight and then washed with hexanes (2 x 100 mL). The aqueous phase was adjusted to pH 2 with 1 N hydrochloric acid and extracted with ethyl ether (3 x 100 mL). The combined organic extracts were washed once with saturated brine (100 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford 12 g (88%) of the title compound as a white solid. MS (FAB) m/e 294 $(M+H)^+$.

Example 6

Preparation of Boc-(±)-2-Amino-5-phenylpentanoic acid

Di-*tert*-butyl dicarbonate (24 g) in 100 mL of *tert*-butanol was added dropwise to a stirred solution of (±)-2-amino-5-phenylpentanoic acid (21 g) dissolved in 150 mL of 1 N sodium hydroxide solution. The solution was stirred at ambient temperature overnight and then washed with hexanes (2 x 100 mL). The aqueous phase was adjusted to pH 2 with 1 N hydrochloric acid and extracted with ethyl ether (3 x 100 mL). The combined organic extracts were washed once with saturated brine (100 mL), dried over magnesium sulfate and concentrated *in vacuo* to

afford 30 g (88%) of the title compound as a white solid. MS (FAB) m/e 294 $(M+H)^+$.

The compounds of Examples 7 through 154 were prepared using standard peptide synthetic methods described above and exemplified in Examples 1 and 2.

Example 7

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-2-fluorobenzyl)-Arginyl-OH

MS (FAB) m/e 558 $(M+H)^+$.

Example 8

N-(5-Methoxyindole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 523 $(M+H)^+$.

Example 9

N-[1-(3-Benzoylaminopropyl)-Indole-2-carbonyl]-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 654 $(M+H)^+$.

Example 10

N-{N-Benzyl-N-(3-phenylpropyl)amino-carbonyl}-Arginyl-OH

MS (FAB) m/e 426 $(M+H)^+$.

Example 11

N-(1-Naphthylcarbonyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 504 $(M+H)^+$.

Example 12

3,5-Dichlorobenzoyl-DCysteinyl[S-3-pyridylmethyl]-Arginyl-OH

MS (FAB) m/e 541 $(M+H)^+$.

Example 13

N-(5-Fluoroindole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 511 $(M+H)^+$.

Example 14

N-(1-[N-{(2R)-2-Amino-3-cyclohexylpropanoyl}aminopropyl]-indole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 703 $(M+H)^+$.

Example 15

N-{N-(2-Phenylethyl)-N-(3-phenylpropyl)amino-carbonyl}-Arginyl-OH

MS (FAB) m/e 440 $(M+H)^+$.

Example 16

N-Benzoyl-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OMe

MS (FAB) m/e 468 $(M+H)^+$.

Example 17

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-2-pyridylmethyl)-Arginyl-OH

MS (FAB) m/e 541 $(M+H)^+$.

Example 18

N-(Pyrrole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-DLArginyl-OH

MS (FAB) m/e 443 $(M+H)^+$.

Example 19

N-Benzoyl-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 454 $(M+H)^+$.

Example 20

N-(Indole-2-carbonyl)-{(S)-3-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 493 $(M+H)^+$.

Example 21

N-(3,4-Dimethylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 482 $(M+H)^+$.

Example 22

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-4-methoxybenzyl)-Arginyl-OH

MS (FAB) m/e 570 $(M+H)^+$.

Example 23

N-(5-Chloro-indole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 527 $(M+H)^+$.

Example 24

N-[1-(3-Aminopropyl)-indole-2-carbonyl]-{(*R*)-2-Amino-5-phenyl-pentanoyl}-Arginyl-OH

MS (FAB) m/e 550 $(M+H)^+$.

Example 25

N-(Indole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-{(S)-3-Amino-6-guanidinohexanoyl}-OH

MS (FAB) m/e 507 $(M+H)^+$.

Example 26

N-(3,5-Dichlorobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 522 $(M+H)^+$.

Example 27

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-4-pyridylmethyl)-Arginyl-OH

MS (FAB) m/e 541 $(M+H)^+$.

Example 28

N-(3-Fluorobenzoyl)-{(*R/S*)-2-Amino-4-phenoxybutanoyl}-Arginyl-OH

MS (FAB) m/e 474 $(M+H)^+$.

Example 29

N-(Indole-2-carbonyl)-(N-Methyl){(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 507 $(M+H)^+$.

Example 30

N-(2-Aminocinnamoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 495 $(M+H)^+$.

Example 31

N-(3,4-Dichlorobenzyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 522 $(M+H)^+$.

Example 32

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-1-phenylethyl)-Arginyl-OH

MS (FAB) m/e 554 $(M+H)^+$.

Example 33

N-(Indole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 493 $(M+H)^+$.

Example 34

{(*R*)-2-(1,2,3,4-Tetrahydro-3-oxopyrrole[3.4.b]indole-2-yl)-5-phenyl-pentanoyl}-Arginyl-OH

MS (FAB) m/e 505 $(M+H)^+$.

Example 35

N-(2-Acetamido-3-phenyl-2-propenoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 537 $(M+H)^+$.

Example 36

N-(2-Naphthylcarbonyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 504 $(M+H)^{\pm}$.

Example 37

N-(Pyridine-2-carbonyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 455 $(M+H)^+$.

Example 38

N-Benzyl-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 440 $(M+H)^+$.

Example 39

N-(1-tert-Butyloxycarbonylmethylindole-2-carbonyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 607 $(M+H)^+$.

Example 40

N-(2-Nitrocinnamoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 525 $(M+H)^+$.

Example 41

N-{N-(4-Phenylbutyl)-N-benzylamino-carbonyl}-Arginyl-OH

MS (FAB) m/e 440 $(M+H)^+$.

Example 42

N-(3,5-Dichlorobenzyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 508 $(M+H)^+$.

Example 43

N-(3-Fluoro-4-methylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-{(S)-3-Guanidino-2-aminopropanoyl}-OH

MS (FAB) m/e 458 $(M+H)^+$.

Example 44

N-(4-Phenylpyrrole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 519 $(M+H)^+$.

Example 45

N-{1-(3-Acetylaminopropyl)indole-2-carbonyl}-{(*R*)-2-Amino-5-phenyl-pentanoyl}-Arginyl-OH

MS (FAB) m/e 592 $(M+H)^+$.

Example 46

N-(4-Trifluoromethylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 522 $(M+H)^+$.

Example 47

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-3-methoxybenzyl)-Arginyl-OH

MS (FAB) m/e 570 $(M+H)^+$.

Example 48

N-{[2-(3-Fluorobenzoyl)-1-(3-phenylpropyl)hydrazino]-carbonyl}-Arginyl-OH

MS (FAB) m/e 473 $(M+H)^+$.

Example 49

N-(1-Benzylindole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 583 $(M+H)^+$.

Example 50

N-[1-(3-Guanidinopropyl)indole-2-carbonyl]-{(*R*)-2-Amino-5-phenyl-pentanoyl}-Arginyl-OH

MS (FAB) m/e 592 $(M+H)^+$.

Example 51

N-(4-n-Butylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 510 $(M+H)^+$.

Example 52

N-(Pyrazine-2-carbonyl)-Arginyl-OH

MS (FAB) m/e 281 $(M+H)^+$.

Example 53

N-{[2-(3-Fluoro-4-methylbenzoyl)-1-(3-phenylpropyl)hydrazino]-carbonyl}-Arginyl-OH

MS (FAB) m/e 487 $(M+H)^+$.

Example 54

N-(Indole-2-carbonyl)-DCysteinyl(S-2-cyanobenzyl)-Arginyl-OH

MS (FAB) m/e 536 $(M+H)^+$.

Example 55

N-{1-[3-(Imidazol-4-ylmethylcarbonylamino)propyl]-indole-2-carbonyl}-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 658 $(M+H)^+$.

Example 56

N-(4-Methylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 468 $(M+H)^+$.

Example 57

N-(Thienyl-2-carbonyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 460 $(M+H)^+$.

Example 58

N-(Indole-2-carbonyl)-DCysteinyl(S-benzyl)-Arginyl-OH

MS (FAB) m/e 511 $(M+H)^+$.

Example 59

N-(2-Chlorobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 488 $(M+H)^+$.

Example 60

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-3-methylbenzyl)-Arginyl-OH

MS (FAB) m/e 554 $(M+H)^+$.

Example 61

N-{[2-(3,4-Difluorobenzoyl)-1-(3-phenylpropyl)hydrazino]-carbonyl}-Arginyl-OH

MS (FAB) m/e 491 $(M+H)^+$.

Example 62

N-(Indole-2-carbonyl)-DCysteinyl(S-4-fluorobenzyl)-Arginyl-OH

MS (FAB) m/e 529 $(M+H)^+$.

Example 63

N-(3-Chlorobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 488 $(M+H)^+$.

Example 64

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-2-methylbenzyl)-Arginyl-OH
MS (FAB) m/e 554 $(M+H)^+$.

Example 65

N-(3,5-Dichlorobenzoyl)-{(*R/S*)-2-Amino-5-phenylpent-2-enoyl}-Arginyl-OH
MS (FAB) m/e 520,522 $(M+H)^+$.

Example 66

N-(Indole-2-carbonyl)-DCysteinyl(S-3-fluorobenzyl)-Arginyl-OH
MS (FAB) m/e 529 $(M+H)^+$.

Example 67

N-(4-Chlorobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 488 $(M+H)^+$.

Example 68

N-{N-(4-Phenylbutyl)-N-(3-phenylpropyl)amino-carbonyl}-Arginyl-OH
MS (FAB) m/e 468 $(M+H)^+$.

Example 69

N-(2-Methylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 468 $(M+H)^+$.

Example 70

N-(3,5-Dichlorobenzoyl)-DSeryl(O-benzyl)-Arginyl-OH
MS (FAB) m/e 524,526 $(M+H)^+$.

Example 71

N-[1(3-Phenylpropyl)indole-2-carbonyl]-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 611 $(M+H)^+$.

Example 72

N-(4-Acetylbenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 496 $(M+H)^+$.

Example 73

N-(3-Methylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 468 $(M+H)^+$.

Example 74

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-4-methylbenzyl)-Arginyl-OH

MS (FAB) m/e 554 $(M+H)^+$.

Example 75

N-(3,5-Dichlorobenzoyl)-D-(3-Benzylsulfinylalanyl)-Arginyl-OH

MS (FAB) m/e 556 $(M+H)^+$.

Example 76

N-(3,5-Difluorobenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 490 $(M+H)^+$.

Example 77

N-(3-Aminomethylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 483 $(M+H)^+$.

Example 78

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-4-chlorobenzyl)-Arginyl-OH

MS (FAB) m/e 574 $(M+H)^+$.

Example 79

N-{[2-(3,5-Dichlorobenzoyl)-1-(3-phenylpropyl)]hydrazino-carbonyl}-Arginyl-OH

MS (FAB) m/e 523 $(M+H)^+$.

Example 80

N-(2-Fluorobenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 472 $(M+H)^+$.

Example 81

N-[3-(6-Aminohexanonylaminomethyl)benzoyl]-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 596 $(M+H)^+$.

Example 82

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-3-chlorobenzyl)-Arginyl-OH

MS (FAB) m/e 574 $(M+H)^+$.

Example 83

N-(3,4-Difluorobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 490 $(M+H)^+$.

Example 84

N-(4-Fluorobenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 472 $(M+H)^+$.

Example 85

N-Benzoyl-DCysteinyl(S-benzyl)-Arginyl-OH

MS (FAB) m/e 472 $(M+H)^+$.

Example 86

N-Benzoyl-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Ornithinyl-OH

MS (FAB) m/e 412 $(M+H)^+$.

Example 87

N-(3-Nitrobenzoyl)-Arginyl-OH
MS (FAB) m/e 324 $(M+H)^+$.

Example 88

N-(3-Fluorobenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 472 $(M+H)^+$.

Example 89

N-(4-tert-Butylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 510 $(M+H)^+$.

Example 90

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-2-chlorobenzyl)-Arginyl-OH
MS (FAB) m/e 574 $(M+H)^+$.

Example 91

N-[2-(6-Aminohexanoyl)tetrahydroisoquinoline-3-carbonyl]-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 622 $(M+H)^+$.

Example 92

N-(3-Chloro-4-methoxybenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 518 $(M+H)^+$.

Example 93

N-Cyclohexylcarbonyl-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 460 $(M+H)^+$.

Example 94

N-(3-Chloro-4-methylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 502 $(M+H)^+$.

Example 95

N-(3,4-Dimethyl-5-ethoxycarbonyl-pyrrole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 543 $(M+H)^+$.

Example 96

N-(4-Methylpentanoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 448 $(M+H)^+$.

Example 97

N-(3,5-Dichlorobenzoyl-DCysteinyl(S-benzyl)-Arginyl-OH
MS (FAB) m/e 540 $(M+H)^+$.

Example 98

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-1-ethoxycarbonylbenzyl)-Arginyl-OH
MS (FAB) m/e 612 $(M+H)^+$.

Example 99

N-(Indole-4-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 493 $(M+H)^+$.

Example 100

N-Benzoyl-{(*R/S*)-2-Amino-5-phenylpentanoyl}-{(S)-6-Guanidino-2-aminohexanoyl}-OH
MS (FAB) m/e 468 $(M+H)^+$.

Example 101

N-(2-Nitrobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 499 $(M+H)^+$.

Example 102

N-(3,5-Dichloro-2-hydroxybenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 538 $(M+H)^+$.

Example 103

N-(Indole-5-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 493 $(M+H)^+$.

Example 104

N-(3,4,5-Trimethoxybenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 544 $(M+H)^+$.

Example 105

N-Tosyl-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 504 $(M+H)^+$.

Example 106

N-(3-Fluoro-4-methylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 486 $(M+H)^+$.

Example 107

N-(Indole-3-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 493 $(M+H)^+$.

Example 108

N-Phenoxyacetyl-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 484 $(M+H)^+$.

Example 109

N-Benzoyl-(N-methyl){(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 468 $(M+H)^+$.

Example 110

N-(3,5-Dichlorobenzoyl)-DCysteinyl[α-(piperazin-2-ylaminocarbonyl)-benzyl]-Arginyl-OH

MS (FAB) m/e 661 $(M+H)^+$.

Example 111

N-(3-Chloro-4-fluorobenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 506 $(M+H)^+$.

Example 112

N-Benzoyl-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Alanyl-OH

MS (FAB) m/e 369 $(M+H)^+$.

Example 113

N-(4-Phenoxybenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 546 $(M+H)^+$.

Example 114

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-benzimidazol-2-ylmethyl)-Arginyl-OH

MS (FAB) m/e 580 $(M+H)^+$.

Example 115

N-(3,5-Dichlorobenzoyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 522 $(M+H)^+$.

Example 116

N-Phenylacetyl-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 468 $(M+H)^+$.

Example 133

N-(3-Bromo-4-methylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 546 $(M+H)^+$.

Example 134

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-α-carboxybenzyl)-Arginyl-OH

MS (FAB) m/e 584 $(M+H)^+$.

Example 135

N-(Pyrrole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 443 $(M+H)^+$.

Example 136

N-(3-Bromobenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 532 $(M+H)^+$.

Example 137

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-3-nitrobenzyl)-Arginyl-OH

MS (FAB) m/e 585 $(M+H)^+$.

Example 138

N-(3-Oxo-2-phenylpyrazole-5-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 536 $(M+H)^+$.

Example 139

N-Benzoyl-Cysteinyl(S-benzyl)-Arginyl-OH

MS (FAB) m/e 472 $(M+H)^+$.

Example 140

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-4-nitrobenzyl)-Arginyl-OH

MS (FAB) m/e 585 $(M+H)^+$.

Example 141

N-(Indole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OMe

MS (FAB) m/e 507 $(M+H)^+$.

Example 142

N-(3-Trifluoromethylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 522 $(M+H)^+$.

Example 143

N-(3,5-Dichlorbenzoyl)-DCysteinyl(S-2-aminobenzyl)-Arginyl-OH

MS (FAB) m/e 555 $(M+H)^+$.

Example 144

N-Benzylaminocarbonyl-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 483 $(M+H)^+$.

Example 145

N-Benzoyl-(Tetrahydroquinoline-3-carbonyl)-Arginyl-OH

MS (FAB) m/e 438 $(M+H)^+$.

Example 146

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-2-nitrobenzyl)-Arginyl-OH

MS (FAB) m/e 585 $(M+H)^+$.

Example 147

2-Phenylhydrazinocarbonyl-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 484 $(M+H)^+$.

Example 148

N-(3,5-Dimethylbenzoyl)-{(*R/S*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH

MS (FAB) m/e 482 $(M+H)^+$.

Example 149

N-(3,5-Dichlorobenzoyl)-{(*R/S*)-2-Aminooctanoyl}-Arginyl-OH
MS (FAB) m/e 488 $(M+H)^+$.

Example 150

N-(Indole-2-carbonyl)-{(*R/S*)-2-Amino-4-phenoxybutanoyl}-Arginyl-OH
MS (FAB) m/e 495 $(M+H)^+$.

Example 151

N-{1-[3-(2,6-Dioxo-1,2,3,6-tetrahydro-4-pyrimidinecarbonylamino)propyl]-indole-2-carbonyl}-{(*R*)-2-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 688 $(M+H)^+$.

Example 152

N-(Indole-2-carbonyl)-{(*R*)-2-Amino-5-phenylpentanoyl}-(N-Methyl)Arginyl-OH
MS (FAB) m/e 507 $(M+H)^+$.

Example 153

N-(Indole-2-carbonyl)-{(*R*)-3-Amino-5-phenylpentanoyl}-Arginyl-OH
MS (FAB) m/e 493 $(M+H)^+$.

Example 154

N-Benzoyl-{(*R/S*)-2-Amino-6-phenylhexanoyl}-Arginyl-OH
MS (FAB) m/e 468 $(M+H)^+$.

The foregoing examples are merely illustrative of the invention and are not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which is defined in the appended claims.

1. A compound of the formula:

A-B-D

or a pharmaceutically acceptable salt thereof wherein

A is R_1-R_2;
B is R_3-R_4-R_5; and
D is R_6-R_7-R_8;

where

R_1 is selected from the group consisting of
hydrogen,
lower alkyl,
cycloalkyl,
(cycloalkyl)alkyl,
aryl,
arylalkyl,
arylalkenyl,
arylhydrazino,
arylalkylamino,
aminoalkyl,
heterocyclic,
(heterocyclic)alkyl, and
hydrogen;

R_2 is selected from the group consisting of
>C=O,
>C=S,
$>CH_2$, and
$>SO_2$

with the proviso that when R_2 is >C=S or $>SO_2$, then R_1 may be hydrogen;

R_3 and R_6 are >N-R_{101} where R_{101} is independently selected from the group consisting of
hydrogen,
lower alkyl, and
arylalkyl;

R_4 is selected from the group consisting of
-$CR_{200}R_{201}$-,
>NR_{101}, and
>C=CHR_{205}, existing in either the *Z*- or *E*-configuration where R_{205} is arylalkyl;

R_5 is selected from the group consisting of
>C=O,
>CH_2, and
-CH_2-C(O)-;

R_7 is -$CR_{210}R_{211}$- ;

R_8 is selected from the group consisting of
hydrogen,
-CH_2-CO_2H, and
-CO_2R_{100} where R_{100} is selected from the group consisting of hydrogen, lower alkyl or arylalkyl;

R_{200} and R_{210} are independently selected from the group consisting of
hydrogen,
lower alkyl, and
arylalkyl;

R_{201} is selected from the group consisting of

(a) $-(CH_2)_3-Z$ where Z is aryl or heterocyclic with the proviso that when Z is heterocyclic, the point of attachment of the $-(CH_2)_3-$ moiety to Z is a ring carbon atom;

(b) $-CH_2-X-CH_2-Z$, where X is selected from the group consisting of >O, >S, and >N-R where R is hydrogen or lower alkyl, and Z is as defined above with the proviso that when Z is heterocyclic, the point of attachment of the $-CH_2-X-CH_2-$ moiety to Z is a ring carbon atom;

(c) $-CH_2-S-CHR_{300}-W$ where W is aryl and R_{300} is selected from the group consisting of carboxy, alkoxycarbonyl and alkyl,

(d) $-CH_2-CH_2-X-W$, where X and W are as defined above,

(e) $-CH_2-C(O)-NR-W$, where W and R are as defined above, and

(f) $-CH_2-Y-C(O)-Z$, where Y is selected from the group consisting of >O and >N-R where Z and R are as defined above with the proviso that when Z is heterocyclic, the point of attachment of the $-CH_2-Y-C(O)-$ moiety to Z is a carbon atom;

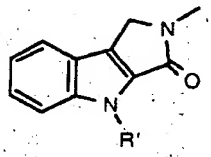
R_{211} is guanidinoalkyl; or

R_1 and R_2, taken together, is selected from the group consisting of

hydrogen,
lower alkyl,
arylalkyl,
aminoalkyl, and
guanidinoalkyl

with the proviso that when R_1 and R_2 taken together s other than arylalkyl, then R_{101} is arylalkyl; or

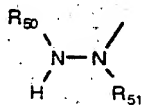
R_1-R_2-R_3, taken together, represent



where R' is selected from hydrogen or loweralkyl; or

R_1-R_2-R_3-R_4, taken together, is selected from the group consisting of

arylalkylamino,
heterocyclic,
arylalkyl and



where R_{50} is aroyl and R_{51} is selected from the group consisting of aryl and arylalkyl.

2. A compound as defined by Claim 1 wherein R_5 is selected from the group consisting of >C=O and >CH_2 and R_3 and R_6 are independently selected from >NH and >N-Methyl.

3. A compound as defined by Claim 1 wherein **B** is 2-amino-5-phenylpentanoyl.

4. A compound as defined by Claim 1 wherein **B** is 2-amino-5-phenylpentanoyl and **D** is Arginyl-OH.

5. A compound as defined by Claim 1, or a pharmaceutically acceptable salt thereof wherein **D** is arginyl-OH selected from he group consisting of:

N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-2-fluorobenzyl)-Arginyl-OH;
N-{N-Benzyl-N-(3-phenylpropyl)amino-carbonyl}-Arginyl-OH;
N-{N-(2-Phenylethyl)-N-(3-phenylpropyl)amino-carbonyl}-Arginyl-OH;
N-{N-(4-Phenylbutyl)-N-benzylamino-carbonyl}-Arginyl-OH;
N-{[2-(3-Fluoro-4-methylbenzoyl)-1-(3-phenylpropyl)-hydrazino]-carbonyl}-Arginyl-OH;
N-(Indole-2-carbonyl)-DCysteinyl(S-benzyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-3-methylbenzyl)-Arginyl-OH;
N-{[2-(3,4-Difluorobenzoyl)-1-(3-phenylpropyl)hydrazino]-carbonyl}-Arginyl-OH;
N-(Indole-2-carbonyl)-DCysteinyl(S-4-fluorobenzyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-2-methylbenzyl)-Arginyl-OH;
N-(Indole-2-carbonyl)-DCysteinyl(S-3-fluorobenzyl)-Arginyl-OH;
N-{N-(4-Phenylbutyl)-N-(3-phenylpropyl)aminocarbony}-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-4-methylbenzyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-4-chlorobenzyl)-Arginyl-OH;
N-{[2-(3,5-Dichlorobenzoyl)-1-(3-phenylpropyl)hydrazino]-carbonyl}-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-3-chlorobenzyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl)-DCysteinyl(S-2-chlorobenzyl)-Arginyl-OH;
N-(3,5-Dichlorobenzoyl-DCysteinyl(S-benzyl)-Arginyl-OH;